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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/291,925	04/14/99	ASHKENAZI	A P1055R1

HM12/0929

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EXAMINER	
ZEMAN,R	
ART UNIT	**PAPER NUMBER**
1645	10

DATE MAILED: 09/29/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/291,925	Ashkenazi et al.
Examiner	**Group Art Unit**
Robert A. Zeman	1645

☒ Responsive to communication(s) filed on *Apr 14, 1999* .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-33* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-33* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *5*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Specification

A substitute specification including claims is required. The substitute specification must have a top margin of at least 2.0 cm (3/4 inch). Please see 37 C.F.R. 1.52(b).

Claim Objections

Claim 9 is objected to because of the following informalities: Said claim contains an obvious grammatical error. Claim has been interpreted to read as "....sequence is operably linked to a pre-sequence associated.....". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 15 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for DNA constructs comprising a first DNA sequence encoding a precursor peptide and a second DNA sequence (encoding a heterologous glycoprotein) operably linked to the first DNA sequence, does not reasonably provide enablement for DNA constructs with additional DNA segments operably linked to the first and second DNA segments. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The specification provides great detail on the construction and use of DNA constructs comprising a first DNA sequence comprising a precursor peptide (the pro sequence of t-PA) which is operably linked to a second DNA sequence encoding a heterologous glycoprotein (TNFR1-IgG1). The specification further discloses the use of sequences for glycosylation site variants as the second DNA segment and methods for the recombinant expression of said DNA constructs *in vitro*. The specification is silent on methods of making **any** DNA construct the consists of more than 2 operably linked DNA sequences. The specification is equally silent on which, additional DNA segments would be "operably-linked" to the first and second segments or how they would be linked. Consequently, it would require **undue** experimentation by one of skill in the art to make and use the claimed invention due to the total lack of guidance within the specification.

Claim 23 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for DNA constructs comprising a first DNA sequence encoding a precursor peptide and a second DNA sequence operably linked to the first DNA segment, wherein the second DNA sequence encodes a heterologous glycosylation site **deletion** variant, does not reasonably provide enablement for DNA constructs comprising a first DNA sequence encoding a precursor peptide and a second DNA sequence operably linked to the first DNA sequence, wherein the second DNA segment encodes a heterologous glycosylation site **addition** variant.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The specification provides great detail on the construction and use of DNA comprising a first DNA sequence comprising a precursor peptide (the pro sequence of t-PA) which is operably linked to a second DNA sequence encoding a heterologous glycoprotein (TNFR1-IgG1). The specification further discloses the use of sequences for glycosylation site variants as the second DNA sequence and methods for the recombinant expression of said DNA constructs *in vitro*. The specification provides great detail in the methods required for the manufacture and use of DNA sequences encoding a heterologous glycosylation site **deletion** variant. The specification discloses that the chimeric proteins generated by the DNA constructs of the instant application contain 4 N-linked glycosylation sites (at amino acid positions 14, 105, 111 and 248) and that said glycosylation sites were "**deleted**" by replacing the codon specifying asparagine in the N-linked carbohydrate attachment sequence with codons specifying glutamine, aspartic acid, asparagine, lysine, serine or threonine thus inactivating the site (see pages 17 and 19). The specification discloses a myriad of different glycosylation site mutants and their secretion efficiencies. However, all the disclosed variants are glycosylation site **deletion** variants. None of the disclosed variants contain more than the 4 N-linked glycosylation sites at amino acid positions 14, 105, 111 and 248. The specification is silent not only on where the additional sites would be located but also on the methods that would be used to achieve such a site addition.

Consequently, it would require **undue** experimentation by one of skill in the art to make and use the claimed invention due to the total lack of guidance within the specification.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 14, 30 and 33 are rendered vague and indefinite by the inconsistent use of the terms "segment" and "sequence". It is unclear whether the "first DNA **segment** encoding the precursor protein" is the same as the "first DNA **sequence**" to which the second DNA segment is operably linked. Consequently, it is impossible to determine the metes and bounds of the claimed invention. It is recommended that consistent terminology be used throughout the claims if "sequence" and "segment" are the same. If they are different, the differences should be clarified.

Claim 29 is rendered vague and indefinite by the use of the phrase "N-linked site at 14 deleted." It is unclear what is meant by "14". Is applicant referring to an amino acid position or some other type chemical nomenclature? As written, it is impossible to determine the metes and bounds of the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Foster et al. (U.S. Patent 5,641,655 IDS-5).

Claim 1 is drawn to a DNA construct comprising a first DNA segment encoding a pro-sequence of mammalian t-PA and a second DNA segment operably linked to the first DNA segment encoding a heterologous glycoprotein. Foster et al. disclose DNA constructs comprising a first DNA segment encoding a secretory peptide (mammalian t-PA) joined to a second DNA segment encoding a heterologous protein (thrombopoietin).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4 and 10-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Foster et al (U.S. Patent 5,641,655 IDS-5) in view of Ashkenazi et al. (PNAS Vol. 88 pages 10535-10539, 1991, IDS-5).

The instant claims are drawn to DNA constructs comprising a first DNA segment encoding a pro-sequence of mammalian t-PA and a second DNA segment operably linked to the first DNA segment encoding a heterologous glycoprotein (TNFR-IgG1). Foster et al. disclose DNA constructs comprising a first DNA segment encoding a secretory peptide (mammalian t-PA) joined to a second DNA segment encoding a heterologous protein (thrombopoietin). The disclosure by Foster et al. differs from the aforementioned claims in that it the heterologous protein encoded by the second DNA segment is thrombopoietin, not TNFR-IgG1. Ashkenazi et al., disclose the sequence for the TNFR-IgG1. Consequently, it would have been obvious for one of skill in the art to use the sequence for TNFR-IgG1 as the second DNA segment in the constructs disclosed by Foster et al. to take advantage of the increased secretion rates associated with the t-PA chimeras disclosed by Foster et al.

Claims 1-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Foster et al (U.S. Patent 5,641,655 IDS-5) in view of Ashkenazi et al. (PNAS Vol. 88 pages 10535-10539, 1991, IDS-5) and Rickles et al. (Journal of Biological Chemistry Vol 263, No. 3 pages 1563-1569, 1988, IDS-5).

The instant claims are drawn to DNA constructs comprising a first DNA segment encoding a pro-sequence of mammalian t-PA and a second DNA segment operably linked to the first DNA segment encoding a heterologous glycoprotein (TNFR-IgG1). Foster et al. disclose DNA constructs comprising a first DNA segment encoding a secretory peptide (mammalian t-PA) joined to a second DNA segment encoding a heterologous protein (thrombopoietin). Foster et al. differs from the aforementioned claims in that the heterologous protein encoded by the second DNA segment is thrombopoietin, not TNFR-IgG1. Additionally, Foster et al. does not disclose the use of non-mammalian t-PA. Ashkenazi et al. disclose the sequence for the TNFR-IgG1. Rickles et al. disclose the sequences for and the uses of murine t-PA in the molecular cloning of complementary DNA. Since Foster et al. disclose that t-PAs from non-human sources can be used in their method, and even listed an example (see column 9 lines 5-9) , it would have been obvious for one of skill in the art to use the sequence for TNFR-IgG1 as the second DNA segment and the non-mammalian t-PA prosequence disclosed by Rickles et al in the constructs disclosed by Foster et al. to take advantage of the increased secretion rates associated with the t-PA pro chimeras disclosed by Foster et al.

Claims 1-4, 10-14, 16-22, and 23-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Foster et al (U.S. Patent 5,641,655 IDS-5) in view of Ashkenazi et al. (PNAS Vol. 88 pages 10535-10539, 1991, IDS-5) and Berman and Lasky et al. (Trends in Biotechnology, Vol. 3, No. 2, pages 51-53, 1985, IDS-5).

The instant claims are drawn to DNA constructs comprising a first DNA segment encoding a pro-sequence of mammalian t-PA and a second DNA segment operably linked to the first DNA segment encoding a heterologous glycoprotein (TNFR-IgG1). Foster et al. disclose DNA constructs comprising a first DNA segment encoding a secretory peptide (mammalian t-PA) joined to a second DNA segment encoding a heterologous protein (thrombopoietin). The disclosure by Foster et al. differs from the aforementioned claims in that the heterologous protein encoded by the second DNA segment is thrombopoietin, not TNFR-IgG1. Additionally, Foster et al. does not disclose the use of glycosylation site variants as the products of the second DNA fragments. Ashkenazi et al. not only discloses the sequence for the TNFR-IgG1, but also potential asparagine-linked (N-linked) glycosylation sites (see Figure 1 on page 10536). Since, as disclosed by Berman and Lasky, N-linked glycosylation plays a role in the solubility half-life and antigenicity of the glycoprotein, it would have been obvious for one of skill in the art to alter the codons for the potential N-linked glycosylation sites in the sequence for TNFR-IgG1 (disclosed by Ashkenazi et al.) and use the resulting sequences as the second DNA segment in the constructs disclosed by Foster et al. The use of the aforementioned "TNFR-IgG1 glycosylation variants" would not only take advantage of the increased secretion rates associated with the t-PA

pro chimeras disclosed by Foster et al. but would allow for the rapid development of recombinant TNFR-IgG1 protein with tailored solubility, half-life and antigenicity properties.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (703) 308-7991. The examiner can be reached between the hours of 7:30 am and 4:00 pm Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, Donna Wortman, Primary Examiner can be reached at (703) 308-1032 or the examiner's supervisor, Lynette Smith, can be reached at (703)308-3909.

DONNA WORTMAN
PRIMARY EXAMINER

Robert A. Zeman

September 28, 2000